S. Huff 09/767,424

PDR® entry for

PEG-Intron™ (Schering)
(Peginterferon alfa-2b)

Powder for Injection

Description

WARNING

Alpha interferons, including PEG-Intron, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many but not all cases these disorders resolve after stopping PEG-Intron therapy. See **WARNINGS** , **ADVERSE REACTIONS** .

DESCRIPTION

PEG-Intron™, peginterferon alfa-2b Powder for Injection, is a covalent conjugate of recombinant alfa interferon with monomethoxy polyethylene glycol (PEG). The molecular weight of the PEG portion of the molecule is 12,000 daltons. The average molecular weight of the PEG-Intron molecule is approximately 31,000 daltons. The specific activity of pegylated interferon alfa-2b is approximately 0.7×10^{8} IU/mg protein.

Interferon alfa-2b, the starting material used to manufacture PEG-Intron, is a water-soluble protein with a molecular weight of 19,271 daltons produced by recombinant DNA techniques. It is obtained from the bacterial fermentation of a strain of *Escherichia coli* bearing a genetically engineered plasmid containing an interferon gene from human leukocytes.

PEG-Intron is a white to off-white lyophilized powder supplied in 2-mL vials for subcutaneous use. Each vial contains either 74 µg, 118.4 µg, 177.6 µg, or 222 µg of

PEG-Intron, and 1.11 mg dibasic sodium phosphate anhydrous, 1.11 mg monobasic sodium phosphate dihydrate, 59.2 mg sucrose and 0.074 mg polysorbate 80. Following reconstitution with 0.7 mL of the supplied diluent (Sterile Water for Injection, USP), each vial contains PEG-Intron at strengths of either 100 µg/mL, 160 µg/mL, 240 µg/mL, or 300 µg/mL.

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CLINICAL PHARMACOLOGY

General: The biological activity of PEG-Intron is derived from its interferon alfa-2b moiety. Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface and initiate a complex sequence of intracellular events. These include the induction of certain enzymes, suppression of cell proliferation, immunomodulating activities such as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells, and inhibition of virus replication in virus-infected cells. Interferon alfa upregulates the Th1 T-helper cell subset in *in vitro* studies. The clinical relevance of these findings is not known.

Pharmacodynamics: PEG-Intron raises concentrations of effector proteins such as serum neopterin and 2'5' oligoadenylate synthetase, raises body temperature, and causes reversible decreases in leukocyte and platelet counts. The correlation between the *in vitro* and *in vivo* pharmacologic and pharmacodynamic and clinical effects is unknown.

Pharmacokinetics: Following a single subcutaneous dose of PEG-Intron, the mean absorption half-life ($t^{1}/_{2}k_{a}$) was 4.6 hours. Maximal serum concentrations (C_{max}) occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours. The C_{max} and AUC measurements of PEG-Intron increase in a dose-related manner. After multiple dosing, there is an increase in bioavailability of PEG-Intron. Week 48 mean trough concentrations (320 pg/mL; range 0, 2960) are approximately 3-fold higher than Week 4 mean trough concentrations (94 pg/mL; range 0, 416). The mean PEG-Intron elimination half-life is approximately 40 hours (range 22 to 60 hours) in patients with HCV infection. The apparent clearance of PEG-Intron is estimated to be approximately 22.0 mL/hr·kg. Renal elimination accounts for 30% of the clearance. Single dose peginterferon alfa-2b pharmacokinetics following a subcutaneous 1.0 µg/kg dose suggest the clearance of peginterferon alfa-2b is reduced by approximately half in patients with impaired renal function (creatinine clearance <50 mL/minute).

Pegylation of interferon alfa-2b produces a product (PEG-Intron) whose clearance is lower than that of non-pegylated interferon alfa-2b. When compared to INTRON A, PEG-Intron (1.0 µg/kg) has approximately a seven-fold lower mean apparent clearance and a five-fold greater mean half-life permitting a reduced dosing frequency. At effective therapeutic doses, PEG-Intron has approximately ten-fold greater C_{max} and 50-fold greater AUC than

· interferon alfa-2b.

Pharmacokinetic data from geriatric patients (> 65 years of age) treated with a single subcutaneous dose of 1.0 µg/kg of PEG-Intron showed no remarkable differences in C_{max}, AUC, clearance, or elimination half-life from those obtained in younger patients.

During the 48 week treatment period with PEG-Intron no differences in the pharmacokinetic profiles were observed between male and female patients with chronic hepatitis C infection.

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Drug Interactions: It is not known if PEG-Intron therapy causes clinically significant drug-drug interactions with drugs metabolized by the liver in patients with hepatitis C. In 12 healthy subjects known to be CYP2D6 extensive metabolizers, a single subcutaneous dose of 1 µg/kg PEG-Intron did not inhibit CYP1A2, 2C8/9, 2D6, hepatic 3A4 or N-acetyltransferase; the effects of PEG-Intron on CYP2C19 were not assessed.

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CLINICAL STUDIES

A randomized study compared treatment with PEG-Intron (0.5, 1.0, or 1.5 µg/kg once weekly SC) to treatment with INTRON A, (3 million units three times weekly SC) in 1219 adults with chronic hepatitis from HCV infection. The patients were not previously treated with interferon alfa, had compensated liver disease, detectable HCV RNA, elevated ALT, and liver histopathology consistent with chronic hepatitis. Patients were treated for 48 weeks and were followed for 24 weeks post-treatment. Seventy percent of all patients were infected with HCV genotype 1, and 74% of all patients had high baseline levels of HCV RNA (more than 2 million copies per mL of serum), two factors known to predict poor response to treatment.

Response to treatment was defined as undetectable HCV RNA and normalization of ALT at 24 weeks post-treatment. The response rates to the 1.0 and 1.5 µg/kg PEG-Intron doses were similar to each other and were both higher than response rates to INTRON A. (See **Table 1**)

TABLE 1. Rates of Response to Treatment

	A PEG-Intron 0.5 µg/kg (N=315)	B PEG-Intron 1.0 µg/kg (N=298)	C INTRON A 3 MIU TIW (N=307)	B-C (95% CI) Difference between PEG-Intron 1.0 µg/kg and INTRON A
Treatment Response (Combined Virologic Response and ALT Normalization)	17%	24%	12%	11 (5, 18)
Virologic Response [a]	18%	25%	12%	12 (6, 9)
ALT Normalization	24%	29%	18%	11 (5, 18)

[a] Serum HCV RNA is measured by a research-based quantitive polymerase chain reaction with a lower limit of detection of 100 copies/mL at the National Genetics Institute, Culver City, CA.

Patients with both viral genotype 1 and high serum levels of HCV RNA at baseline were less likely to respond to treatment with PEG-Intron. Among patients with the two unfavorable prognostic variables, 8% (12/157) responded to PEG-Intron treatment and 2% (4/169) responded to INTRON A. Doses of PEG-Intron higher than the recommended dose did not result in higher response rates in these patients.

Patients receiving PEG-Intron with viral genotype 1 had a response rate of 14% (28/199) while patients with other viral genotypes had a 45% (43/96) response rate.

Ninety-six percent of the responders in the PEG-Intron groups and 100% of responders in the INTRON A group first cleared their viral RNA by week 24 of treatment. See **DOSAGE AND ADMINISTRATION** .

The treatment response rates were similar in men and women. Response rates were lower in African American and Hispanic patients and higher in Asians compared to Caucasians. Although African Americans had a higher proportion of poor prognostic factors compared to Caucasians the number of non-Caucasians studied (9% of the total) was insufficient to

allow meaningful conclusions about differences in response rates after adjusting for prognostic factors.

Liver biopsies were obtained before and after treatment in 60% of patients. A modest reduction in inflammation compared to baseline that was similar in all four treatment groups was observed.

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INDICATIONS AND USAGE

PEG-Intron, peginterferon alfa-2b, monotherapy is indicated for the treatment of chronic hepatitis C in patients not previously treated with interferon alpha who have compensated liver disease and are at least 18 years of age. The safety and efficacy of peginterferon alfa-2b (PEG-Intron) in combination with ribavirin (REBETOL) for the treatment of chronic hepatitis C have not been established.

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CONTRAINDICATIONS

PEG-Intron is contraindicated in patients with:

- hypersensitivity to PEG-Intron or any component of the product
- autoimmune hepatitis
- decompensated liver disease

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WARNINGS

Patients should be monitored for the following serious conditions, some of which may become life threatening. Patients with persistently severe or worsening signs or symptoms should be withdrawn from therapy.

Neuropsychiatric events

Life-threatening or fatal neuropsychiatric events, including suicide, suicidal and homicidal ideation, depression, relapse of drug addiction/overdose, and aggressive behavior have occurred in patients with and without a previous psychiatric disorder during PEG-Intron treatment and follow-up. Psychoses and hallucinations have been observed in patients treated with alpha interferons. PEG-Intron should be used with extreme caution in patients with a history of psychiatric disorders. Patients should be advised to report immediately any symptoms of depression and/or suicidal ideation to their prescribing physicians. Physicians

- should monitor all patients for evidence of depression and other psychiatric symptoms. In severe cases, PEG-Intron should be stopped immediately and psychiatric intervention instituted.

Bone marrow toxicity

PEG-Intron suppresses bone marrow function, sometimes resulting in severe cytopenias. PEG-Intron should be discontinued in patients who develop severe decreases in neutrophil or platelet counts. Very rarely alpha interferons may be associated with aplastic anemia. (See **DOSAGE AND ADMINISTRATION**)

Endocrine disorders

PEG-Intron causes or aggravates hypothyroidism and hyperthyroidism. Hyperglycemia has been observed in patients treated with PEG-Intron. Diabetes mellitus has been observed in patients treated with alpha interferons. Patients with these conditions who cannot be effectively treated by medication should not begin PEG-Intron therapy. Patients who develop these conditions during treatment and cannot be controlled with medication should not continue PEG-Intron therapy.

Cardiovascular events

Cardiovascular events, which include hypotension, arrhythmia, tachycardia, cardiomyopathy, and myocardial infarction have been observed in patients treated with PEG-Intron. PEG-Intron should be used cautiously in patients with cardiovascular disease. Patients with a history of myocardial infarction and arrhythmic disorder who require PEG-Intron therapy should be closely monitored (see **Laboratory tests**).

Colitis

Fatal and nonfatal ulcerative and hemorrhagic colitis has been observed within 12 weeks of the start of alpha interferon treatment. Abdominal pain, bloody diarrhea, and fever are the typical manifestations. PEG-Intron treatment should be discontinued immediately in patients who develop these symptoms and signs. The colitis usually resolves within 1-3 weeks of discontinuation of alpha interferons.

Pancreatitis

Fatal and nonfatal pancreatitis has been observed in patients treated with alpha interferon. PEG-Intron therapy should be suspended in patients with signs and symptoms suggestive of pancreatitis and discontinued in patients diagnosed with pancreatitis.

Autoimmune disorders

- Development or exacerbation of autoimmune disorders (e.g., thyroiditis, thrombocytopenia, rheumatoid arthritis, interstitial nephritis, systemic lupus erythematosus, psoriasis) have been observed in patients receiving PEG-Intron. PEG-Intron should be used with caution in patients with autoimmune disorders.

Pulmonary disorders

Dyspnea, pulmonary infiltrates, pneumonitis and pneumonia, some resulting in patient deaths, have been associated with PEG-Intron or alpha interferon therapy. Patients with pulmonary infiltrates or pulmonary function impairment should be closely monitored.

Hypersensitivity

Serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed during alpha interferon therapy. If such a reaction develops during treatment with PEG-Intron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

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PRECAUTIONS

- PEG-Intron has not been studied in patients who have failed other alpha interferon treatments.
- The safety and efficacy of PEG-Intron for the treatment of hepatitis C in patients who have received liver or other organ transplant recipients have not been studied.
- The safety and efficacy of PEG-Intron for the treatment of patients with HCV coinfected with HIV or HBV have not been established.

Ophthalmologic disorders: Retinal hemorrhages, cotton wool spots, and retinal artery or vein obstruction have been observed after treatment with PEG-Intron or alpha interferons. Patients who have diabetes mellitus or hypertension should have eye examinations before the start of PEG-Intron treatment.

Patients with renal failure: Patients with impairment of renal function should be closely monitored for signs and symptoms of interferon toxicity and doses of PEG-Intron should be adjusted accordingly. PEG-Intron should be used with caution in patients with creatinine clearance <50 mL/min. See **DOSAGE AND ADMINISTRATION** .

Immunogenicity: One percent of patients (7/734) receiving PEG-Intron developed low-titer (</=64) neutralizing antibodies to INTRON A. The clinical and pathological significance of the appearance of serum neutralizing antibodies is unknown. No apparent correlation of antibody development to clinical response or adverse events was observed. The incidence of post-treatment binding antibody was approximately 10% for patients

receiving PEG-Intron and approximately 15% for patients receiving INTRON A. The data reflect the percentage of patients whose test results were considered positive for antibodies to PEG-Intron in a Biacore assay that is used to measure binding antibodies, and in an antiviral neutralization assay which measures serum neutralizing antibodies. The percentage of patients whose test results were considered positive for antibodies is highly dependent on the sensitivity and specificity of the assays. Additionally the observed incidence of antibody positivity in these assays may be influenced by several factors including sample timing and handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to PEG-Intron with the incidence of antibodies to other products may be misleading.

Laboratory Tests: PEG-Intron may cause severe decreases in neutrophil and platelet counts, and abnormality of TSH. In 10% of patients treated with PEG-Intron ALT levels rose 2 to 5-fold above baseline. The elevations were transient and were not associated with deterioration of other liver functions.

Patients on PEG-Intron therapy should have hematology and blood chemistry testing before the start of treatment and then periodically thereafter. In the clinical trial CBC (including neutrophil and platelet counts) and chemistries (including AST, ALT, and bilirubin) were measured during the treatment period at weeks 2, 4, 8, 12, and then at 6-week intervals or more frequently if abnormalities developed. TSH levels were measured every 12 weeks during the treatment period.

Patients who have pre-existing cardiac abnormalities should have electrocardiograms administered before treatment with PEG-Intron.

Information for Patients: Patients receiving PEG-Intron should be directed in its appropriate use, informed of the benefits and risks associated with treatment, and referred to the **MEDICATION GUIDE** .

A puncture-resistant container for the disposal of used syringes and needles should be supplied to the patient for at home use. Patients should be thoroughly instructed in the importance of proper disposal and cautioned against any reuse of needles and syringes. The full container should be disposed of according to the directions provided by the physician (see **MEDICATION GUIDE**).

Patients should be informed that there are no data evaluating whether PEG-Intron therapy will prevent transmission of HCV infection to others. Also, it is not known if treatment with PEG-Intron will cure hepatitis C or prevent cirrhosis, liver failure, or liver cancer that may be the result of infection with the hepatitis C virus.

Patients should be advised that laboratory evaluations are required before starting therapy and periodically thereafter (see **Laboratory Tests**). It is advised that patients be well-hydrated, especially during the initial stages of treatment. "Flu-like" symptoms

associated with administration of PEG-Intron may be minimized by bedtime administration of PEG-Intron or by use of antipyretics.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: PEG-Intron has not been tested for its carcinogenic potential.

Mutagenesis: Neither PEG-Intron, nor its components interferon or methoxypolyethylene glycol caused damage to DNA when tested in the standard battery of mutagenesis assays, in the presence and absence of metabolic activation.

Impairment of Fertility: Irregular menstrual cycles were observed in female cynomolgus monkeys given subcutaneous injections of 4239 $\mu g/m^2$ PEG-Intron every other day for one month, at approximately 345 times the recommended weekly human dose (based upon body surface area). These effects included transiently decreased serum levels of estradiol and progesterone, suggestive of anovulation. Normal menstrual cycles and serum hormone levels resumed in these animals 2 to 3 months following cessation of PEG-Intron treatment. Every other day dosing with 262 $\mu g/m^2$ (approximately 21 times the weekly human dose) had no effects on cycle duration or reproductive hormone status. The effects of PEG-Intron on male fertility have not been studied.

Pregnancy Category C: Non-pegylated Interferon alfa-2b, has been shown to have abortifacient effects in *Macaca mulatta* (rhesus monkeys) at 15 and 30 million IU/kg (estimated human equivalent of 5 and 10 million IU/kg, based on body surface area adjustment for a 60 kg adult). PEG-Intron should be assumed to also have abortifacient potential. There are no adequate and well-controlled studies in pregnant women. PEG-Intron therapy is to be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Therefore, PEG-Intron is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Nursing Mothers: It is not known whether the components of PEG-Intron are excreted in human milk. Because of the potential for adverse reactions from the drug in nursing infants, a decision must be made whether to discontinue nursing or discontinue the treatment, taking into account the importance of the product to the mother.

Pediatric Use Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

Geriatric Patients Clinical studies of PEG-Intron did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, treatment with alpha interferons, including PEG-Intron, is associated with CNS, cardiac, and systemic (flu-like) adverse

effects. Because these adverse reactions may be more severe in the elderly, caution should be exercised in use of PEG-Intron in this population. This drug is known to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, the risk of toxic reactions to this drug may be greater in patients with impaired renal function.

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ADVERSE REACTIONS

Nearly all study patients experienced one or more adverse events. The incidence of serious adverse events was similar (about 12%) in all treatment groups. In many but not all cases, events resolve after stopping PEG-Intron therapy. Some patients continued to experience adverse events for several months after discontinuation of therapy. There was one patient death, a suicide, among patients receiving PEG-Intron and two patient deaths in the INTRON A group (1 murder/suicide and 1 sudden death). Overall, 10% of patients in the PEG-Intron groups discontinued therapy due to adverse events compared to 6% in the INTRON A group. Fourteen percent of patients in the PEG-Intron groups required dose reduction compared to 6% in the INTRON A group.

The most common adverse events associated with PEG-Intron were "flu-like" symptoms which occurred in approximately 50% of patients, and may decrease in severity as treatment continues. Application site disorders occurred frequently (47%) and included injection site inflammation, and reaction (i.e. bruise, itchiness, irritation). Injection site pain was reported in 2% of patients receiving PEG-Intron. Alopecia (thinning of the hair) is also often associated with PEG-Intron.

Fifty-seven percent of patients treated with PEG-Intron experienced psychiatric adverse events, most commonly depression (29%). Suicidal behavior (ideation, attempts, and suicides) occurred in 1% of all patients during or shortly after treatment with PEG-Intron. (See **WARNINGS**).

Patients receiving PEG-Intron appeared to experience a greater number of adverse events (e.g., injection site reaction, fever, rigors, nausea) compared to patients receiving INTRON A. The number of adverse events in all body systems in general was higher in patients receiving the higher PEG-Intron dosages.

Adverse events that occurred in the Phase 3 clinical trial at >/=5% incidence are provided in **Table 2** by treatment group.

TABLE 2. Adverse Events Occurring in >/=5% of Patients

	PEG-Intron 1.0 µg/kg	INTRON A 3 MIU

Adverse Events	(N=297)	(N=303)
Percentage of Patients Reporting Adverse Events *		
Application Site Disorders		
Injection Site Inflammation/Reaction	47	20
Autonomic Nervous System Disorders		
Flushing	6	3
Sweating Increased	6	7
Body as a Whole--General Disorders		
Headache	56	52
Fatigue	52	54
Influenza-Like Symptoms	46	38
Rigors	23	19
Fever	22	12
Weight Decrease	11	13
RUQ pain	8	8
Malaise	7	6
Central and Peripheral Nervous System Disorders		
Dizziness	12	10
Hypertonia	5	3
Endocrine Disorders		
Hypothyrodism	5	3
Gastro-intestinal System Disorders		
Nausea	26	20
Anorexia	20	17
Diarrhea	18	16
Abdominal Pain	15	11
Vomiting	7	6
Dyspepsia	6	7
Hematologic Disorders		
Neutropenia	6	2
Thrombocytopenia	7	<1
Infectious Disorders		
Infection Viral	11	10
Liver and Biliary System Disorders		
Hepatomegaly	6	5

Musculoskeletal System Disorders		
Musculoskeletal Pain	56	58
Psychiatric Disorders		
Depression	29	25
Insomnia	23	23
Anxiety/Emotional Lability/Irritability	28	34
Respiratory System Disorders		
Pharyngitis	10	7
Sinusitis	7	7
Coughing	6	5
Skin and Appendages Disorders		
Alopecia	22	22
Pruritus	12	8
Dry skin	11	9
Rash	6	7
* Patients reporting one or more adverse events. A patient may have reported more than one adverse event within a body system/organ class category.		

Numerous adverse events were observed at a frequency <5%. In the absence of a non-treatment control group the relationship to study drug could not be determined.

Individual serious adverse events occurred at a frequency </=1% and included suicide attempt, suicidal ideation, severe depression; relapse of drug addiction/overdose; nerve palsy (facial, oculomotor); cardiomyopathy, myocardial infarction, retinal ischemia, retinal vein thrombosis, transient ischemic attack, supraventricular arrhythmias, loss of consciousness; neutropenia, infection (pneumonia, abscess); autoimmune thrombocytopenia, hyperthyroidism, rheumatoid arthritis, interstitial nephritis, lupus-like syndrome, aggravated psoriasis; urticaria.

Laboratory Values

Neutrophils Neutrophil counts decreased in 70% of patients. Severe potentially life-threatening neutropenia ($<0.5 \times 10^9$/L) occurred in 1% of patients.

Platelets Platelet counts decreased in 20% of patients. Treatment with PEG-Intron resulted in severe decreases in platelet counts ($<50{,}000/mm^3$) in 1% of patients.

The incidence and severity of thrombocytopenia and neutropenia were greater in the

- PEG-Intron groups compared to the interferon alfa group. Platelet and neutrophil counts generally returned to pretreatment levels within 4 weeks of the cessation of therapy.

Thyroid Function TSH abnormalities developed in 16% of patients and were associated with clinically apparent hypothyroidism (5%) or hyperthyroidism (1%). Subjects developed new onset TSH abnormalities while on treatment and during the follow-up period. At the end of the follow-up period 7% of subjects still had abnormal TSH values.

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OVERDOSAGE

There is limited experience with overdosage. In the clinical study, 13 patients accidentally received a dose greater than that prescribed. There were no instances in which a patient received more than 2.5 times the intended dose. The maximum dose received by any patient was 3.45 µg/kg weekly over a period of approximately 12 weeks. There were no serious reactions attributed to these overdosages.

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DOSAGE AND ADMINISTRATION

A patient should self-inject only if the physician determines that it is appropriate and the patient agrees to medical follow-up as necessary and training in proper injection technique has been given to him/her. (See illustrated **MEDICATION GUIDE** for instructions.)

PEG-Intron is administered subcutaneously once weekly for one year. The dose should be administered on the same day of each week. Initial dosing should be based on weight as described in **Table 3.**

TABLE 3. Recommended Dosing

Vial Strength * to Use (µg/mL)	Weight (kg)	Amount of PEG-Intron to Administer (µg)	Volume of PEG-Intron * to Administer (mL)
100	37-45	40	0.4
	46-56	50	0.5
160	57-72	64	0.4
	73-88	80	0.5
240	89-106	96	0.4
	107-136	120	0.5
300	137-160	150	0.5

* When reconstituted as directed

Serum HCV RNA levels should be assessed after 24 weeks of treatment. Discontinuation of treatment should be considered in any patient who has not achieved an HCV RNA below the limit of detection of the assay after 24 weeks of therapy with PEG-Intron. (See **CLINICAL STUDIES**.)

There are no safety and efficacy data for treatment longer than 48 weeks or for re-treatment of patients who relapse following PEG-Intron therapy.

Dose Reduction

If a serious adverse reaction develops during the course of treatment (see **WARNINGS**) discontinue or modify the dosage of PEG-Intron to one-half the starting dosage until the adverse event abates or decreases in severity. If persistent or recurrent intolerance develops despite adequate dosage adjustment, discontinue treatment with PEG-Intron. For dose modification in the event of neutropenia and thrombocytopenia see **Table 4.**

TABLE 4. Guidelines for Dose Modifications for Neutropenia and Thrombocytopenia

	Dose Reduction	Permanent Discontinuation
Neutrophil Count	$<0.75 \times 10^9$/L	$<0.50 \times 10^9$/L
Platelet Count	$<80 \times 10^9$/L	$<50 \times 10^9$/L

Preparation and Administration

- Two B-D Safety Lok™ syringes are provided in the package; one syringe is for the reconstitution steps and one for the patient injection. There is a plastic safety sleeve to be pulled over the needle after use. The syringe locks with an audible click when the green stripe on the safety sleeve covers the red stripe on the needle. Brief instructions for the preparation and administration of PEG-Intron Powder for Injection are provided below. Please refer to the **MEDICATION GUIDE** for detailed, step by step instructions.

Reconstitute the PEG-Intron lyophilized product with only 0.7 mL of supplied diluent (Sterile Water for Injection, USP). **The diluent vial is for single use only. The remaining diluent should be discarded.** No other medications should be added to solutions containing PEG-Intron, and PEG-Intron should not be reconstituted with other diluents. Swirl gently to hasten complete dissolution of the powder. The reconstituted solution should be clear and colorless. Visually inspect the solution for particulate matter and discoloration prior to administration. The solution should not be used if discolored or cloudy, or if particulates are present. (See **MEDICATION GUIDE** for detailed instructions).

The reconstituted solution should be used immediately and cannot be stored for more than 24 hours at 2°-8°C (see **Storage**). The appropriate PEG-Intron dose should be withdrawn and injected subcutaneously. (See **MEDICATION GUIDE** for detailed instructions.) The PEG-Intron vial is a single use vial and does not contain a preservative. **DO NOT REENTER VIAL. DISCARD UNUSED PORTION.** Once the dose from a single dose vial has been withdrawn, the sterility of any remaining product can no longer be guaranteed. Pooling of unused portions of some medications has been linked to bacterial contamination and morbidity.

After preparation and administration of the PEG-Intron injection, it is essential to follow the procedure for proper disposal of syringes and needles. A puncture-resistant container should be used for disposal of syringes. Patients should be instructed in the technique and importance of proper syringe disposal and be cautioned against reuse of these items (see **MEDICATION GUIDE** for detailed instructions.)

Storage

PEG-Intron, should be stored at 25°C (77°F): excursions permitted to 15-30°C (59-86°F)[see USP Controlled Room Temperature]. After reconstitution with supplied Diluent the solution should be used immediately, but may be stored up to 24 hours at 2° to 8°C (36° to 46°F). The reconstituted solution contains no preservative, is clear and colorless. **Do not freeze.**

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HOW SUPPLIED

PEG-Intron is a white to off-white lyophilized powder supplied in 2-mL vials. The

- PEG-Intron Powder for Injection should be reconstituted with 0.7 mL of the supplied Diluent (Sterile Water for Injection, USP) prior to use.

	Each PEG-Intron Package Contains:	
For Patients 37-56 kg	A box containing one 100 µg/mL vial of PEG-Intron Powder for Injection and one 5 mL vial of Diluent (Sterile Water for Injection, USP), 2 B-D Safety Lok™ syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1368-01)
For Patients 57-88 kg	A box containing one 160 µg/mL vial of PEG-Intron Powder for Injection and one 5 mL vial of Diluent (Sterile Water for Injection, USP), 2 B-D Safety Lok™ syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1291-01)
For Patients 89-136 kg	A box containing one 240 µg/mL vial of PEG-Intron Powder for Injection and one 5 mL vial of Diluent (Sterile Water for Injection, USP), 2 B-D Safety Lok™ syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1304-01)
For Patients 137-160 kg	A box containing one 300 µg/mL vial of PEG-Intron Powder for Injection and one 5 mL vial of Diluent (Sterile Water for Injection, USP), 2 B-D Safety Lok™ syringes with a safety sleeve and 2 alcohol swabs.	(NDC 0085-1279-01)

Schering Corporation

Kenilworth, NJ 07033 USA

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Stedman's Definition

Enter a word or phrase to search for. (HINT: Highlight a word with the mouse and use copy and paste)

S, Huff 09/767,424

PDR® entry for

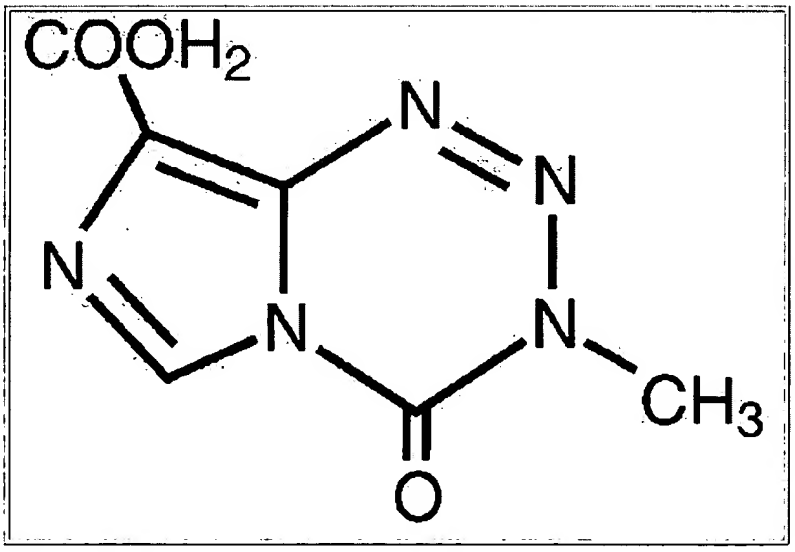
TEMODAR™ (Schering)
(temozolomide)

CAPSULES

Description

DESCRIPTION

TEMODAR Capsules for oral administration contain temozolomide, an imidazotetrazine derivative. The chemical name of temozolomide is 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]- *as* -tetrazine-8-carboxamide. The structural formula is:



The material is a white to light tan/light pink powder with a molecular formula of $C_6H_6N_6O_2$ and a molecular weight of 194.15. The molecule is stable at acidic pH (<5), and labile at pH >7, hence can be administered orally. The prodrug, temozolomide, is rapidly hydrolysed to the active 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC) at

neutral and alkaline pH values, with hydrolysis taking place even faster at alkaline pH.

Each capsule contains either 5 mg, 20 mg, 100 mg, or 250 mg of temozolomide. The inactive ingredients for TEMODAR Capsules are lactose anhydrous, colloidal silicon dioxide, sodium starch glycolate, tartaric acid, and stearic acid. Gelatin capsule shells contain titanium dioxide. The capsules are imprinted with pharmaceutical ink.

TEMODAR 5 mg: green imprint contains pharmaceutical grade shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide, titanium dioxide, yellow iron oxide, and FD&C Blue #2 aluminum lake.

TEMODAR 20 mg: brown imprint also contains pharmaceutical grade shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, purified water, ammonium hydroxide, potassium hydroxide, titanium dioxide, black iron oxide, yellow iron oxide, brown iron oxide, and red iron oxide.

TEMODAR 100 mg: blue imprint contains pharmaceutical glaze (modified) in an ethanol/shellac mixture, isopropyl alcohol, n-butyl alcohol, propylene glycol, titanium dioxide, and FD&C Blue #2 aluminum lake.

TEMODAR 250 mg: black, imprint contains pharmaceutical grade shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, purified water, ammonium hydroxide, potassium hydroxide, and black iron oxide.

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CLINICAL PHARMACOLOGY

Mechanism of Action: Temozolomide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound MTIC. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O^6 and N^7 positions at guanine.

Pharmacokinetics: Temozolomide is rapidly and completely absorbed after oral administration; peak plasma concentrations occur in 1 hour. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and T_{max} increased 2-fold (from 1.1 to 2.25 hours) when temozolomide was administered after a modified high-fat breakfast. Temozolomide is rapidly eliminated with a mean elimination half-life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range. Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%.

Metabolism and Elimination: Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC) and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC) which is known to be an intermediate in purine and nucleic acid biosynthesis and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. Relative to the AUC of temozolomide, the exposure to MTIC and AIC is 2.4% and 23%, respectively. About 38% of the administered temozolomide total radioactive dose is recovered over 7 days; 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is as unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolite(s) (17%). Overall clearance of temozolomide is about 5.5 L/hr/m ^{2}.

Special Populations: *Age* Population pharmacokinetic analysis indicates that age (range 19 to 78 years) has no influence on the pharmacokinetics of temozolomide. In the anaplastic astrocytoma study population, patients 70 years of age or older had a higher incidence of Grade 4 neutropenia and Grade 4 thrombocytopenia in the first cycle of therapy than patients under 70 years of age (see **PRECAUTIONS**). In the entire safety database, however, there did not appear to be a higher incidence in patients 70 years of age or older (see **ADVERSE REACTIONS**).

Gender Population pharmacokinetic analysis indicates that women have an approximately 5% lower clearance (adjusted for body surface area) for temozolomide than men. Women have higher incidences of Grade 4 neutropenia and thrombocytopenia in the first cycle of therapy than men (see **ADVERSE REACTIONS**).

Race The effect of race on the pharmacokinetics of temozolomide has not been studied.

Tobacco Use Population pharmacokinetic analysis indicates that the oral clearance of temozolomide is similar in smokers and nonsmokers.

Creatinine Clearance Population pharmacokinetic analysis indicates that creatinine clearance over the range of 36-130 mL/min/m ^{2} has no effect on the clearance of temozolomide after oral administration. The pharmacokinetics of temozolomide have not been studied in patients with severely impaired renal function (CLcr < 36 mL/min/m ^{2}). Caution should be exercised when TEMODAR is administered to patients with severe renal impairment. TEMODAR has not been studied in patients on dialysis.

Hepatically Impaired Patients In a pharmacokinetic study, the pharmacokinetics of temozolomide in patients with mild-to-moderate hepatic impairment (Child's-Pugh Class I - II) were similar to those observed in patients with normal hepatic function. Caution should be exercised when temozolomide is administered to patients with severe hepatic impairment.

Pediatrics Pediatric patients (3 to 17 years of age) and adult patients have similar clearance and half-life values for temozolomide. There is no clinical experience with the use of TEMODAR in children under the age of 3 years.

Drug-Drug Interactions In a multiple-dose study, administration of TEMODAR with ranitidine did not change the C_{max} or AUC values for temozolomide or MTIC.

Population analysis indicates that administration of valproic acid decreases the clearance of temozolomide by about 5% (see **PRECAUTIONS**).

Population analysis failed to demonstrate any influence of coadministered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H_2 -receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

Clinical Studies: A single-arm, multicenter study was conducted in 162 patients who had anaplastic astrocytoma at first release and who had a baseline Karnofsky performance status of 70 or greater. Patients had previously received radiation therapy and may also have previously received a nitrosourea with or without other chemotherapy. Fifty-four patients had disease progression on prior therapy with both a nitrosourea and procarbazine and their malignancy was considered refractory to chemotherapy (refractory anaplastic astrocytoma population). Median age of this subgroup of 54 patients was 42 years (19 to 76). Sixty-five percent were male. Seventy-two percent of patients had a KPS of >/=80. Sixty-three percent of patients had surgery other than a biopsy at the time of initial diagnosis. Of those patients undergoing resection, 73% underwent a subtotal resection and 27% underwent a gross total resection. Eighteen percent of patients had surgery at the time of first relapse. The median time from initial diagnosis to first relapse was 13.8 months (4.2 to 75.4).

TEMODAR was given for the first 5 consecutive days of a 28-day cycle at a starting dose of 150 mg/m^2/day. If the nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil count was >/=1.5 × 10^9/L (1,500/μL) and the nadir and Day 29, Day 1 of next cycle, platelet count was >/=100 × 10^9/L (100,000/μL), the TEMODAR dose was increased to 200 mg/m^2/day for the first 5 consecutive days of a 28-day cycle.

In the refractory anaplastic astrocytoma population the overall tumor response rate (CR + PR) was 22% (12/54 patients) and the complete response rate was 9% (5/54 patients). The median duration of all responses was 50 weeks (range of 16 to 114 weeks) and the median duration of complete responses was 64 weeks (range of 52 to 114 weeks). In this population, progression-free survival at 6 months was 45% (95% confidence interval 31% to 58%) and progression-free survival at 12 months was 29% (95% confidence interval 16% to 42%). Median progression-free survival was 4.4 months. Overall survival at 6 months was 74% (95% confidence interval 62% to 86%) and 12-month overall survival was 65% (95% confidence interval 52% to 78%). Median overall survival was 15.9 months.

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INDICATIONS AND USAGE

TEMODAR (temozolomide) Capsules are indicated for the treatment of adult patients with refractory anaplastic astrocytoma, ie, patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine.

This indication is based on the response rate in the indicated population. No results are available from randomized controlled trials in recurrent anaplastic astrocytoma that demonstrate a clinical benefit resulting from treatment, such as improvement in disease-related symptoms, delayed disease progression, or improved survival.

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CONTRAINDICATIONS

TEMODAR (temozolomide) Capsules are contraindicated in patients who have a history of hypersensitivity reaction to any of its components. TEMODAR is also contraindicated in patients who have a history of hypersensitivity to DTIC, since both drugs are metabolized to MTIC.

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WARNINGS

Patients treated with TEMODAR may experience myelosuppression. Prior to dosing, patients must have an absolute neutrophil count (ANC) >/=1.5 × 10^9/L and a platelet count >/=100 × 10^9/L. A complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above 1.5 × 10^9/L and platelet count exceeds 100 × 10^9/L. In the clinical trials, if the ANC fell to <1.0 × 10^9/L or the platelet count was <50 × 10^9/L during any cycle, the next cycle was reduced by 50 mg/m^2, but not below 100 mg/m^2. Patients who do not tolerate 100 mg/m^2 should not receive TEMODAR. Geriatric patients and women have been shown in clinical trials to have a higher risk of developing myelosuppression. Myelosuppression generally occurred late in the treatment cycle. The median nadirs occurred at 26 days for platelets (range 21 to 40 days) and 28 days for neutrophils (range 1 to 44 days). Only 14% (22/158) of patients had a neutrophil nadir and 20% (32/158) of patients had a platelet nadir which may have delayed the start of the next cycle. Neutrophil and platelet counts returned to normal, on average, within 14 days of nadir counts (see **PRECAUTIONS**).

Pregnancy: Temozolomide may cause fetal harm when administered to a pregnant woman. Five consecutive days of oral administration of 75 mg/m^2/day in rats and 150 mg/m^2/day

in rabbits during the period of organogenesis (3/8 and 3/4 the maximum recommended human dose, respectively) caused numerous malformations of the external organs, soft tissues, and skeleton in both species. Doses of 150 mg/m ^{2} /day in rats and rabbits also caused embryolethality as indicated by increased resorptions. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with TEMODAR.

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PRECAUTIONS

Information for Patients: In clinical trials, the most frequently occurring adverse effects were nausea and vomiting. These were usually either self-limiting or readily controlled with standard antiemetic therapy. Capsules should not be opened. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes. The medication should be kept away from children and pets.

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Drug Interaction: Administration of valproic acid decreases oral clearance of temozolomide by about 5%. The clinical implication of this effect is not known.

Patients with Severe Hepatic or Renal Impairment: Caution should be exercised when TEMODAR is administered to patients with severe hepatic or renal impairment (see **Special Populations**).

Geriatrics: Clinical studies of temozolomide did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Caution should be exercised when treating elderly patients.

In the anaplastic astrocytoma study population, patients 70 years of age or older had a higher incidence of Grade 4 neutropenia and Grade 4 thrombocytopenia (2/8; 25%, p=.31 and 2/10; 20%, p=.09, respectively) in the first cycle of therapy than patients under 70 years of age (see **ADVERSE REACTIONS**).

Laboratory Tests: A complete blood count should be obtained on Day 22 (21 days after the first dose). Blood counts should be performed weekly until recovery if the ANC falls below 1.5×10^9 /L and the platelet count falls below 100×10^9 /L.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Standard carcinogenicity studies were not conducted with temozolomide. In rats treated with 200 mg/m ^{2} temozolomide (equivalent to the maximum recommended daily human dose) on 5 consecutive days every 28 days for 3 cycles, mammary carcinomas were found in both males and females. With 6 cycles of treatment at 25, 50, and 125 mg/m ^{2} (about 1/8 to 1/2 the maximum recommended daily human dose), mammary carcinomas were observed at all doses and fibrosarcomas of the heart, eye, seminal vesicles, salivary glands, abdominal cavity, uterus, and prostate; carcinoma of the seminal vesicles, schwannoma of the heart, optic nerve, and harderian gland; and adenomas of the skin, lung, pituitary, and thyroid were observed at the high dose.

Temozolomide was mutagenic *in vitro* in bacteria (Ames assay) and clastogenic in mammalian cells (human peripheral blood lymphocyte assays).

Reproductive function studies have not been conducted with temozolomide. However, multicycle toxicology studies in rats and dogs have demonstrated testicular toxicity (syncytial cells/immature sperm, testicular atrophy) at doses of 50 mg/m ^{2} in rats and 125 mg/m ^{2} in dogs (1/4 and 5/8, respectively, of the maximum recommended human dose on a body surface area basis).

Pregnancy Category D: See **WARNINGS** section.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from TEMODAR, patients receiving TEMODAR should discontinue nursing.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

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ADVERSE REACTIONS

Tables 1 and **2** show the incidence of adverse events in the 158 patients in the anaplastic astrocytoma study for whom data are available. In the absence of a control group, it is not clear in many cases whether these events should be attributed to temozolomide or the patients' underlying conditions, but nausea, vomiting, fatigue, and hematologic effects appear to be clearly drug related. The most frequently occurring side effects were nausea, vomiting, headache, and fatigue. The adverse events were usually NCI Common Toxicity Criteria (CTC) Grade 1 or 2 (mild to moderate in severity) and were self-limiting, with nausea and vomiting readily controlled with antiemetics. The incidence of severe nausea and vomiting (CTC Grade 3 or 4) was 10% and 6%, respectively. Myelosuppression (thrombocytopenia and neutropenia) was the dose-limiting adverse event. It usually occurred

within the first few cycles of therapy and was not cumulative.

Myelosuppression occurred late in the treatment cycle and returned to normal, on average, within 14 days of nadir counts. The median nadirs occurred at 26 days for platelets (range 21 to 40 days) and 28 days for neutrophils (range 1 to 44 days). Only 14% (22/158) of patients had a neutrophil nadir and 20% (32/158) of patients had platelet nadir which may have delayed the start of the next cycle (see **WARNINGS**). Less than 10% of patients required hospitalization, blood transfusion, or discontinuation of therapy due to myelosuppression.

In clinical trial experience with 110 to 111 women and 169 to 174 men (depending on measurements), there were higher rates of Grade 4 neutropenia (ANC < 500 cells/μL) and thrombocytopenia (< 20,000 cells/μL) in women than men in the first cycle of therapy: (12% versus 5% and 9% versus 3%, respectively).

In the entire safety database for which hematologic data exist (N=932), 7% (4/61) and 9.5% (6/63) of patients over age 70 experienced Grade 4 neutropenia or thrombocytopenia in the first cycle, respectively. For patients less than or equal to age 70, 7% (62/871) and 5.5% (48/879) experienced Grade 4 neutropenia or thrombocytopenia in the first cycle, respectively.

Table 1
Adverse Events in the Anaplastic Astrocytoma Trial (>/=5%)

	No. (%) of TEMODAR Patients (N=158)	
	All Events	**Grade 3/4**
Any Adverse Event	**153 (97)**	**79 (50)**
Body as a Whole		
Headache	65 (41)	10 (6)
Fatigue	54 (34)	7 (4)
Asthenia	20 (13)	9 (6)
Fever	21 (13)	3 (2)
Back pain	12 (8)	4 (3)
Cardiovascular		
Edema peripheral	17 (11)	1 (1)
Central and Peripheral Nervous System		
Convulsions	36 (23)	8 (5)
Hemiparesis	29 (18)	10 (6)

Dizziness	19 (12)	1 (1)
Coordination abnormal	17 (11)	2 (1)
Amnesia	16 (10)	6 (4)
Insomnia	16 (10)	0
Paresthesia	15 (9)	1 (1)
Somnolence	15 (9)	5 (3)
Paresis	13 (8)	4 (3)
Urinary incontinence	13 (8)	3 (2)
Ataxia	12 (8)	3 (2)
Dysphasia	11 (7)	1 (1)
Convulsions local	9 (6)	0
Gait abnormal	9 (6)	1 (1)
Confusion	8 (5)	0
Endocrine		
Adrenal hypercorticism	13 (8)	0
Gastrointestinal System		
Nausea	84 (53)	16 (10)
Vomiting	66 (42)	10 (6)
Constipation	52 (33)	1 (1)
Diarrhea	25 (16)	3 (2)
Abdominal pain	14 (9)	2 (1)
Anorexia	14 (9)	1 (1)
Metabolic		
Weight increase	8 (5)	0
Musculoskeletal System		
Myalgia	8 (5)	
Psychiatric Disorders		
Anxiety	11 (7)	1 (1)
Depression	10 (6)	0
Reproductive Disorders		
Breast pain, female	4 (6)	
Resistance Mechanism Disorders		
Infection viral	17 (11)	0
Respiratory System		
Upper respiratory tract infection	13 (8)	0

Pharyngitis	12 (8)	0
Sinusitis	10 (6)	0
Coughing	8 (5)	0
Skin and Appendages		
Rash	13 (8)	0
Pruritus	12 (8)	2 (1)
Urinary System		
Urinary tract infection	12 (8)	0
Micturition increased frequency	9 (6)	0
Vision		
Diplopia	8 (5)	0
Vision Abnormal *	8 (5)	
*Blurred vision, visual deficit, vision changes, vision troubles.		

Table 2
Adverse Hematologic Effects (Grade 3 to 4) in the Anaplastic Astrocytoma Trial

	TEMODAR [a]
Hemoglobin	7/158 (4%)
Neutrophils	20/142 (14%)
Platelets	29/156 (19%)
WBC	18/158 (11%)

[a] Change from Grade 0 to 2 at baseline to Grade 3 or 4 during treatment.

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OVERDOSAGE

Doses of 500, 750, 1,000, 1,250 mg/m ^{2} (total dose per cycle over 5 days) have been evaluated clinically in patients. Dose-limiting toxicity was hematologic and was reported at 1,000 mg/m ^{2} and at 1,250 mg/m ^{2}. Up to 1,000 mg/m ^{2} has been taken as a single dose, with only the expected effects of neutropenia and thrombocytopenia resulting. In the event of an overdose, hematologic evaluation is needed. Supportive measures should be provided as necessary.

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DOSAGE AND ADMINISTRATION

Dosage of TEMODAR must be adjusted according to nadir neutrophil and platelet counts in the previous cycle and neutrophil and platelet counts at the time of initiating the next cycle. The initial dose is 150 mg/m ^{2} orally once daily for 5 consecutive days per 28-day treatment cycle. If both the nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil counts (ANC) are >/=1.5 × 10 ^{9} /L (1,500/μL) and both the nadir and Day 29, Day 1 of next cycle platelet counts are >/=100 × 10 ^{9} /L (100,000/μL), the TEMODAR dose may be increased to 200 mg/m ^{2} /day for 5 consecutive days per 28-day treatment cycle. During treatment, a complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above 1.5 × 10 ^{9} /L (1,500/μL) and the platelet count exceeds 100 × 10 ^{9} /L (100,000/μL). The next cycle of TEMODAR should not be started until the ANC and platelet count exceed these levels. If the ANC falls to <1.0 × 10 ^{9} /L (1,000/μL) or the platelet count is <50 × 10 ^{9} /L (50,000/μL) during any cycle, the next cycle should be reduced by 50 mg/m ^{2} , but not below 100 mg/m ^{2} , the lowest recommended dose (see **Table 3**) (see **WARNINGS**).

TEMODAR therapy can be continued until disease progression. In the clinical trial, treatment could be continued for a maximum of 2 years; but the optimum duration of therapy is not known. For TEMODAR dosage calculations based on body surface area (BSA), see **Table 4** . For suggested capsule combinations based on daily dose, see **Table 5** .

Table 3 Dosing Modification Table

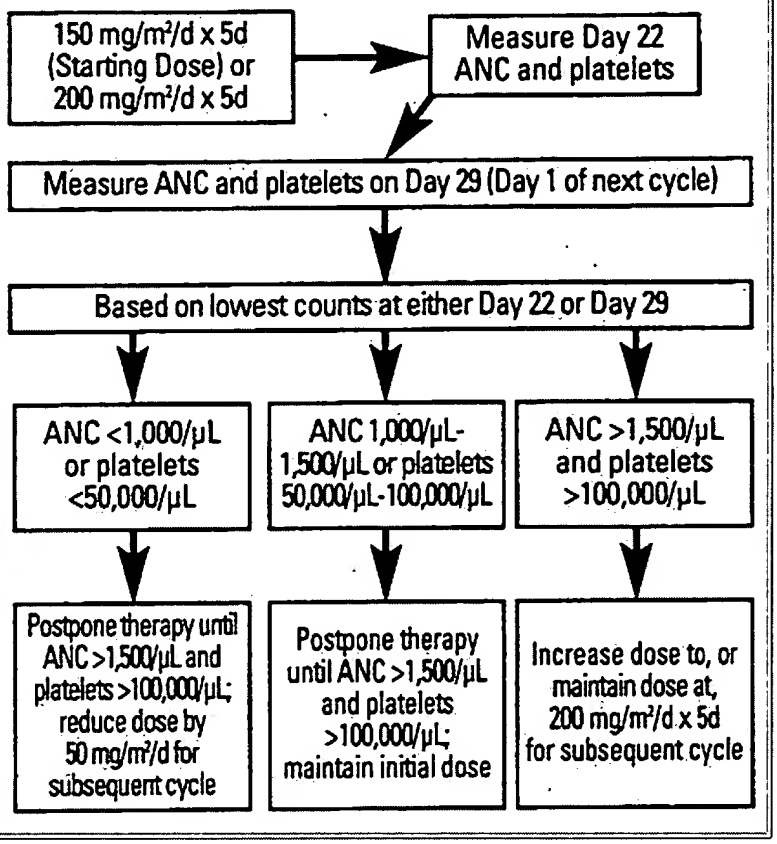

Table 4
Daily Dose Calculations by Body Surface Area (BSA)
for 5 consecutive days per 28-day treatment cycle for
the initial chemotherapy cycle (150 mg/m ^{2}) and for
subsequent chemotherapy cycles (200 mg/m ^{2}) for
patients whose nadir and day of dosing (Day 29, Day 1
of next cycle) absolute neutrophil count (ANC) is >1.5
× 10 ^{9} /L (1,500/µL) and whose nadir and Day 29, Day 1
of next cycle platelet count is >100 × 10 ^{9} /L (100,000/µL).

Total BSA (m^2)	150 mg/m^2 (mg daily)	200 mg/m^2 (mg daily)
0.5	75	100
0.6	90	120
0.7	105	140
0.8	120	160
0.9	135	180
1.0	150	200
1.1	165	220
1.2	180	240
1.3	195	260
1.4	210	280
1.5	225	300
1.6	240	320
1.7	255	340
1.8	270	360
1.9	285	380
2.0	300	400
2.1	315	420
2.2	330	440
2.3	345	460
2.4	360	480
2.5	375	500

Table 5

Suggested Capsule Combinations Based on Daily Dose

	Number of Daily Capsules by Strength (mg)			
Total Daily Dose (mg)	**250**	**100**	**20**	**5**
200	0	2	0	0
205	0	2	0	1
210	0	2	0	2
215	0	2	0	3
220	0	2	1	0

225	0	2	1	1
230	0	2	1	2
235	0	2	1	3
240	0	2	2	0
245	0	2	2	1
250	1	0	0	0
255	1	0	0	1
260	1	0	0	2
265	1	0	0	3
270	1	0	1	0
275	1	0	1	1
280	1	0	1	2
285	1	0	1	3
290	1	0	2	0
295	1	0	2	1
300	0	3	0	0
305	0	3	0	1
310	0	3	0	2
315	0	3	0	3
320	0	3	1	0
325	0	3	1	1
330	1	0	4	0
335	1	0	4	1
340	0	3	2	0
345	0	3	2	1
350	1	1	0	0
355	1	1	0	1
360	1	1	0	2
365	1	1	0	3
370	1	1	1	0
375	1	1	1	1
380	1	1	1	2
385	1	1	1	3
390	1	1	2	0
395	1	1	2	1
400	0	4	0	0

405	0	4	0	1
410	0	4	0	2
415	0	4	0	3
420	0	4	1	0
425	0	4	1	1
430	1	1	4	0
435	0	4	1	3
440	0	4	2	0
445	0	4	2	1
450	1	2	0	0
455	1	2	0	1
460	1	2	0	2
465	1	2	0	3
470	1	2	1	0
475	1	2	1	1
480	1	2	1	2
485	1	2	1	3
490	1	2	2	0
495	1	2	2	1
500	2	0	0	0

In the clinical trial, TEMODAR was administered under both fasting and nonfasting conditions; however, absorption is affected by food (see **CLINICAL PHARMACOLOGY**) and consistency of administration with respect to food is recommended. There are no dietary restrictions with temozolomide. To reduce nausea and vomiting, temozolomide should be taken on an empty stomach. Bedtime administration may be advised. Antiemetic therapy may be administered to and/or following administration of TEMODAR.

TEMODAR (temozolomide) Capsules should not be opened or chewed. They should be swallowed whole with a glass of water.

Handling and Disposal: Temozolomide causes the rapid appearance of malignant tumors in rats. Capsules should not be opened. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes. Procedures for proper handling and disposal of anticancer drugs should be considered. [1-7] Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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HOW SUPPLIED

TEMODAR (temozolomide) Capsules are supplied in amber glass bottles with child-resistant polypropylene caps containing the following capsule strengths:

TEMODAR (temozolomide) Capsules 5 mg: 5 and 20 capsule bottles.

5 count -- NDC 0085-1248-01

20 count -- NDC 0085-1248-02

TEMODAR (temozolomide) Capsules 20 mg: 5 and 20 capsule bottles.

5 count -- NDC 0085-1244-01

20 count -- NDC 0085-1244-02

TEMODAR (temozolomide) Capsules 100 mg: 5 and 20 capsule bottles.

5 count -- NDC 0085-1259-01

20 count -- NDC 0085-1259-02

TEMODAR (temozolomide) Capsules 250 mg: 5 and 20 capsule bottles.

5 count -- NDC 0085-1252-01

20 count -- NDC 0085-1252-02

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

[See USP Controlled Room Temperature]

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